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Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine

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ABSTRACT

Several studies have demonstrated the effectiveness of ketamine in rapidly alleviating depression and suicidal ideation. Intense research efforts have been undertaken to expose the precise mechanism underlying the antidepressant action of ketamine; however, the translation of findings into new clinical treatments has been slow. This translational gap is partially explained by a lack of understanding of the function of time and circadian timing in the complex neurobiology around ketamine. Indeed, the acute pharmacological effects of a single ketamine treatment last for only a few hours, whereas the antidepressant effects peak at around 24 hours and are sustained for the following few days. Numerous studies have investigated the acute and long-lasting neurobiological changes induced by ketamine; however, the most dramatic and fundamental change that the brain undergoes each day is rarely taken into consideration. Here, we explore the link between sleep and circadian regulation and rapid-acting antidepressant effects and summarize how diverse phenomena associated with ketamine's antidepressant actions – such as cortical excitation, synaptogenesis, and involved molecular determinants – are intimately connected with the neurobiology of wake, sleep, and circadian rhythms. We review several recently proposed hypotheses about rapid antidepressant actions, which focus on sleep or circadian regulation, and discuss their implications for ongoing research. Considering these aspects may be the last piece of the puzzle necessary to gain a more comprehensive understanding of the effects of rapid-acting antidepressants on the brain.

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Abbreviations: AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; BMAL1, brain and muscle ARNT-like protein 1; CREB, cAMP related element binding protein; CLOCK, Circadian Locomotor Output Cycles Kaput; CRY, cryptochrome; EEG, electroencephalography; ENCORE-D, encoding consolidation and renormalization in depression; ERK, extracellular-signal

1. Introduction

The discovery of the antidepressant effects of ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, has been an important breakthrough in psychiatry. Whereas weeks of continuous treatment are required for the conventional antidepressant drugs (e.g., fluoxetine, a serotonin-selective reuptake inhibitor) to produce their full therapeutic effects (Rush et al., 2006), ketamine alleviates the core symptoms of depression and suicidal ideation within only a few hours (Aan Het Rot, Zarate, Charney, & Mathew, 2012; Pennybaker, Niciu, Luckenbaugh, & Zarate, 2017). Remarkably, ketamine has also demonstrated rapid therapeutic efficacy in certain other psychiatric disorders, including post-traumatic stress disorder (Feder et al., 2014) and obsessive compulsive disorder (Rodriguez et al., 2013; Rodriguez, Kegeles, Flood, & Simpson, 2011). Last year, the S(+)-enantiomer of ketamine (esketamine) (Zheng et al., 2020) was approved by the US Food and Drug Administration and the European Medicines Agency as an adjunctive treatment for high-suicide-risk, depressed patients to provide faster symptomatic relief. The market entry of esketamine as an intranasal product is expected to increase the use of ketamine in psychiatry, and it has already been included in the depression treatment guidelines, at least in Finland. However, a significant proportion of patients do not get sufficient benefit from ketamine (Aan Het Rot et al., 2012). Moreover, the antidepressant effects of ketamine are transient and commonly persist for only up to a week (Aan Het Rot et al., 2012; Coyle & Laws, 2015; Newport et al., 2015; Pennybaker et al., 2017). Therefore, understanding the neurobiological basis of ketamine's antidepressant effects is essential to improve the treatment protocols and to develop therapies that more reliably lead to rapid and sustained antidepressant effects.

We begin this review by briefly outlining certain effects and mechanisms considered to be important for ketamine's antidepressant action. Although mechanistic studies have identified specific molecular interactions, signaling cascades, synaptic changes, and certain metabolic byproducts of ketamine to be necessary and sufficient for ketamine's antidepressant effects in animals, such insights have not been efficiently translated into clinical treatments. We believe that this translational gap is related to a traditional mindset, wherein ketamine's effects are predominantly explained by basic pharmacological principles and inconspicuous disregard of intrinsic physiology. However, the acute pharmacological effects of ketamine last only a few hours, while its therapeutic effects persist long thereafter. Notably, the antidepressant effects typically peak around 24 hours after a single dose of ketamine (Aan Het Rot et al., 2012; Berman et al., 2000; Coyle & Laws, 2015; Kishimoto et al., 2016; Zarate Jr et al., 2006). We believe that it is important to view the actions of ketamine through a neurobiological perspective, which better appreciates the most fundamental aspects of the circadian physiology of humans. To this end, we discuss the basic neurobiology and function of sleep and circadian rhythm, with a special emphasis on features previously associated with the antidepressant effects of ketamine. Finally, we discuss how recently proposed hypotheses of rapid antidepressant action, which focus on sleep and chronobiology, may provide critical and more comprehensive insights into the actions of rapid-acting antidepressants in the brain.

2. Antidepressant mechanisms of ketamine

The main pharmacological effects of ketamine are mediated through the blockade of NMDARs, which are $\text{Na}^+/\text{Ca}^{2+}/\text{K}^+$ permeable channels activated by the principal excitatory neurotransmitter glutamate. Ketamine also targets various other receptors and channels, and inhibits monoamine reuptake (for a thorough review of ketamine's pharmacology, see Zanos et al., 2018). The effects of ketamine are dose dependent, with the higher end of the range producing a significant blockade of excitatory neurotransmission, ultimately leading to dissociative anesthesia and loss of consciousness. In the treatment of depression, ketamine

is commonly used at lower subanesthetic doses, administered either via a slow intravenous infusion or intranasally. Notably, both in rodents and humans, these subanesthetic doses increase cortical excitation and energy metabolism (Abdallah et al., 2018; Abdallah, Sanacora, Duman, & Krystal, 2018; Breier, Malhotra, Pinals, Weisenfeld, & Pickar, 1997; Li et al., 2016; Lu et al., 2008), which contradicts the anticipated effects of an NMDAR-blocking agent.

The disinhibition hypothesis explains the paradoxical excitatory effects of subanesthetic ketamine through the blockade of NMDARs on gamma-aminobutyric acid (GABA)-ergic interneurons, leading to the disinhibition of pyramidal neurons, accompanied by enhanced glutamate release and burst (Abdallah, Sanacora, et al., 2018; Homayoun & Moghaddam, 2007; Miller, Moran, & Hall, 2016; Zanos & Gould, 2018). Two recent animal studies provide strong support for this hypothesis (Ali et al., 2020; Widman & McMahon, 2018). Among other putative (or complementary) mechanisms, ketamine has been proposed to directly antagonize the extrasynaptic NMDARs on pyramidal neurons (Abdallah, Sanacora, et al., 2018; Miller et al., 2016; Zanos & Gould, 2018) and to block NMDAR-mediated spontaneous neurotransmission (Autry et al., 2011). Moreover, animal studies suggest that ketamine exerts NMDAR inhibition-independent antidepressant actions via its hydroxynorketamine metabolites (HNKs; especially 2R,6R-HNK) (Zanos et al., 2016). This hypothesis is not, however, unequivocally supported by preclinical data (Yamaguchi et al., 2018; Yang et al., 2017). Furthermore, recent clinical studies have observed a negative – rather than a positive – correlation with the plasma levels of 2R,6R-HNK and antidepressant and antisuicidal effects of ketamine (Farmer et al., 2020; Grunebaum et al., 2019).

Most hypotheses about ketamine's antidepressant action ultimately converge on its ability to activate postsynaptic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) through a glutamate burst (Koike, Iijima, & Chaki, 2011; Li et al., 2010; Maeng et al., 2008). In line with this notion, pre- and cotreatment with an AMPAR inhibitor blocks the antidepressant-like behavioral effects of ketamine in rodents (Autry et al., 2011; Li et al., 2010; Maeng et al., 2008). The ketamine metabolite HNK also promotes glutamate release and AMPAR activation in mice (Pham et al., 2018), effects that may arise – at least in part – through the blockade of presynaptic metabotropic glutamate receptor subtype 2 (mGlu₂) inhibitory autoreceptors (Zanos et al., 2019). Notably, AMPAR-positive allosteric modulators exhibit antidepressant effects; – however, their therapeutic effects may need chronic administration (Mendez-David et al., 2017; Nations et al., 2012; Shen et al., 2019), implying that their effects more closely resemble those of conventional antidepressants.

The ketamine-induced activation of AMPARs is associated with several important molecular pathways implicated in antidepressant actions. Most importantly, ketamine evokes the rapid translation and release of brain-derived neurotrophic factor (BDNF) (Autry et al., 2011; Lepack, Bang, Lee, Dwyer, & Duman, 2016), a neurotrophin known for its pivotal role in synaptic plasticity (Park & Poo, 2013; Song, Martinowich, & Lee, 2017) and antidepressant effects (Castrén, Vöikar, & Rantamäki, 2007; Duman, Heninger, & Nestler, 1997). Ketamine also increases the phosphorylation of the BDNF receptor TrkB (Autry et al., 2011; Sun et al., 2016); however, these effects are most prominent with high (sedative-anesthetic) doses (Kohtala et al., 2019). Nevertheless, the antidepressant-like effects of subanesthetic ketamine and several novel, putative, rapid-acting antidepressants are diminished in BDNF^{met66met} knock-in mice that exhibit compromised activity-dependent BDNF release (Fukumoto et al., 2019; Ghosal et al., 2018; Kato et al., 2018; Liu et al., 2012). It has been suggested that, through its effects on BDNF-TrkB signaling, ketamine utilizes molecular mechanisms that ultimately reverse synaptic deficits and thereby alter network activity – features implicated in the pathophysiology of depression (Duman & Aghajanian, 2012).

Downstream of TrkB, mammalian target of rapamycin (mTOR) and extracellular signal-regulated kinase 1/2 (ERK1/2, also known as p44/

42-mitogen-activated protein kinase [p44/42-MAPK]) signaling along with the inhibition of glycogen synthase kinase 3 β (GSK3 β) are considered important for ketamine's antidepressant action (Autry et al., 2011; Autry & Monteggia, 2012; Beurel, Song, & Joje, 2011; Duman & Aghajanian, 2012; Dwyer, Maldonado-Avilés, Lepack, DiLeone, & Duman, 2015; Rantamäki & Yalcin, 2016; Réus et al., 2014). Moreover, ketamine increases the transcription of immediate-early genes (IEGs), such as Homer-1a, which further contribute to glutamatergic signaling and synaptic function (De Bartolomeis et al., 2013; Ficek et al., 2016). Notably, in rodents, the upregulation of Homer-1a in association with the onset of antidepressant-like effects are a common feature of several antidepressant treatments (Holz et al., 2019; Serchov et al., 2015). BDNF up-regulates Homer-1a mRNA and its protein accumulation at synapses in cultured neurons, presumably through the ERK pathway (Ji et al., 2010; Kato, Fukazawa, Ozawa, Inokuchi, & Sugiyama, 2003; Sato, Suzuki, & Nakanishi, 2001). The ketamine-induced increase in synapse-associated proteins and dendritic spine formation are causally associated with increased mTOR activity (Duman & Aghajanian, 2012; Li et al., 2010). Indeed, in rodents, the blockade of mTOR signaling with rapamycin abolishes ketamine-induced synaptogenesis along with the associated antidepressant-like behavioral responses (Li et al., 2010; Li et al., 2011). However, a recent study suggests that the increase in prefrontal cortical spine formation is not required for the rapid effects of ketamine on animal behavior or circuit function but may instead contribute to the sustained antidepressant effects (Moda-Sava et al., 2019). The interpretation of these findings and the specific role of mTOR in ketamine's antidepressant actions are complicated by a recent clinical study, in which rapamycin pretreatment – in contrast to the predicted results – prolonged the antidepressant effects of ketamine (Abdallah et al., 2020).

Taking into consideration the direct involvement of the above-mentioned effectors in both – early and late – phases of long-term potentiation (LTP; for review, see Baltaci, Mogulkoc, & Baltaci, 2019), ketamine is expected to affect synaptic plasticity. Indeed, studies employing animal models of depression, such as chronic mild stress, have demonstrated the impairment of hippocampal LTP (Alfarez, Joëls, & Krugers, 2003; Pavlides, Nivón, & McEwen, 2002), which may be restored by ketamine-induced facilitation of BDNF signaling and synaptic plasticity (Ma et al., 2017; Nosyreva et al., 2013; Sun et al., 2016; Zhou et al., 2014). Several studies also support the notion of impaired LTP-like plasticity in depressed patients (Kuhn et al., 2016; Normann, Schmitz, Fürmaier, Döing, & Bach, 2007; Player et al., 2013) and the ability of ketamine to enhance LTP-mediated neural plasticity (Nugent, Wills, Gilbert, & Zarate, 2019; Sumner et al., 2020). Here, increased neural activation is likely the first step towards synaptic change, as demonstrated in rodent studies in which ketamine administration into the infralimbic prefrontal cortex or the optogenetic activation of this area induces antidepressant-like behavioral responses, whereas prior neuronal inactivation with the GABA_A agonist muscimol blocks these effects (Fuchikami et al., 2015). Similarly, the delivery of neutralizing BDNF antibodies into the medial PFC (mPFC) blocks ketamine's antidepressant-like effects (Lepack, Fuchikami, Dwyer, Banasr, & Duman, 2014). More recent rodent studies indicate that the optogenetic stimulation of dopamine receptor 1 expressing pyramidal neurons in the mPFC is sufficient to produce antidepressant-like effects comparable to those of ketamine (Hare et al., 2019).

As demonstrated by this brief overview, the knowledge of ketamine's many effects at various levels is increasing at an astonishing rate. In the following chapters, we discuss how many of the effects associated with ketamine's antidepressant actions, such as

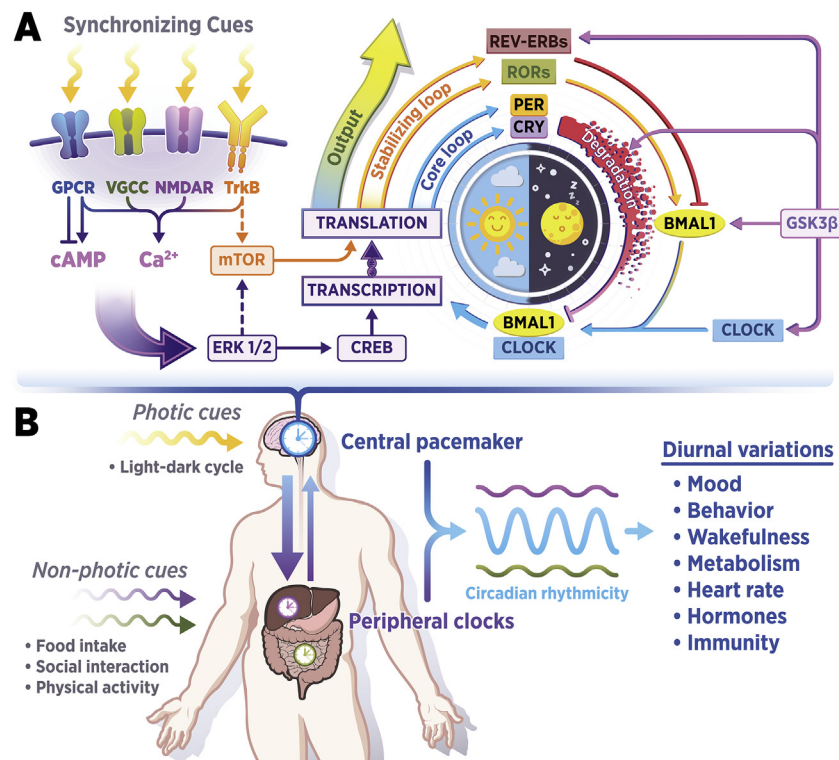
cortical excitation, synaptogenesis, and involved molecular determinants, are physiological events that have a reciprocal connection with wake and sleep. To ensure a good understanding of the topic, we first introduce the basic neurobiology and functions of circadian rhythm and sleep.

3. A primer for time and timing

3.1. Introduction to circadian rhythms and sleep

Animals adjust and coordinate their behavior according to the circadian (Lat. *circa*, approximately; Lat. *dies*, day) rhythms generated by circadian oscillators throughout the body (INFOBOX). The circadian regulation has evolved as an adaptation to temporally align behaviors to the availability of light and nutrients, reflecting the day/night cycle generated by the rotation of the Earth. A multitude of physiological processes, such as body temperature, liver metabolism, energy metabolism, blood pressure, urine production, and neuroendocrine function show circadian rhythmicity (Bass & Takahashi, 2010; Takahashi & Zatz, 1982). Mammalian circadian regulation is hierarchical and comprises a master clock, located in the hypothalamic suprachiasmatic nucleus (SCN), and peripheral clocks, the circadian activity of which is coordinated by the master clock (Moore & Eichler, 1972; Stephan & Zucker, 1972; Yamazaki, 2000; Yoo et al., 2004). The master clock is synchronized to the surrounding environment primarily through photic input from the retina (Challet, Caldelas, Graff, & Pévet, 2003; Pickard, 1980), along with several non-photic inputs related to metabolic activity and vigilance states (Abrahamson & Moore, 2001; Janik & Mrosovsky, 1994; Krout, Kawano, Mettenleiter, & Loewy, 2002; Moga & Moore, 1997; Morin & Allen, 2006), as well as through an endocrine feedback loop mediated by melatonin (Lavie, 1997). The SCN is composed of synchronized ensembles of highly interconnected GABA- and peptidergic neurons, making its oscillations resilient to perturbations resulting from misaligned internal and external cues (Hastings & Herzog, 2004; Liu et al., 2007). In contrast, with a few exceptions, the non-SCN oscillators generally maintain their circadian rhythmicity only in the presence of synchronizing cues from the SCN (Abe et al., 2002) and are also responsive to local cues related to tissue function (Richards & Gumz, 2012). Notably, the lateral habenula is directly connected to the SCN and may display both intrinsic oscillations and direct responses to retinal light (Langel, Ikeno, Yan, Nunez, & Smale, 2018; Mendoza, 2017; Riemann, Krone, Wulff, & Nissen, 2020). At the molecular level, cells generate an approximately 24-hour rhythmicity in response to synchronizing cues by a complex architecture of interlocking positive and negative feedback loops of circadian gene transcription and translation (Partch, Green, & Takahashi, 2014; Takahashi, 2017). The INFOBOX provides a more comprehensive description of the molecular machinery of circadian clockwork. In brief, the cues received by the circadian clocks are relayed primarily through excitatory glutamatergic neurotransmission. Once the cells receive a cue, various Ca²⁺-based signaling pathways are activated, eventually leading to the activation of Ca²⁺/cAMP response element-binding protein (CREB). Subsequently, CREB initiates transcription of various IEGs and clock-controlled genes, possibly resulting in secondary effects throughout the body as systemic signals pass information between individual clocks. The combined synchronized output of the circadian clocks, residing virtually in every tissue throughout the body, enables the organism to anticipate the imminent rhythmic changes in the environment (e.g., light and nutrients) and match them with the appropriate local gene and protein output, eventually resulting in systemic responses (e.g., vigilance states and metabolism).

Infobox



A crash course to circadian rhythms. A. Simplified representation of the intracellular pathways entraining the mammalian circadian clock. The central pacemaker in the suprachiasmatic nucleus (SCN) aligns its circadian fluctuations of gene transcription and translation primarily on the basis of photic input relayed from the retina via excitatory glutamatergic neurotransmission. A light pulse results in an influx of Ca^{2+} into SCN neurons, primarily through the N-methyl-D-aspartate receptors (NMDAR). The same intracellular pathways are also evoked by other means of altering the intracellular Ca^{2+} concentration, including uptake through voltage-gated calcium channels (VGCC) and mobilization of intracellular Ca^{2+} stores. Individual SCN neurons receive additional network input through various G-protein coupled receptors (GPCR; e.g., vasoactive intestinal peptide [VIP], and γ -aminobutyric acid [GABA]) with varying effects on neuronal excitation depending on receptor and ligand. Through a set of kinases, especially extracellular signal-regulated kinase 1/2 (ERK1/2), the pathways affected by incoming signals eventually result in the activation of Ca^{2+} /cAMP response element binding protein (CREB) to promote the transcription of immediate-early genes (e.g. *c-Fos*, *Bdnf*) and clock-controlled genes, leading to altered function and output of the circadian clock. Periodic oscillatory activity of the circadian clockwork arises from the cyclical fluctuations in the levels of circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1) that initiate the transcription and translation of period (*Per1–3*) and cryptochrome (*Cry1–2*) genes. Levels of PER and CRY proteins peak in the daytime to provide negative feedback to CLOCK-BMAL1 activity, thereby suppressing their own transcription. During the subsequent night, PER and CRY degrade gradually, relieving the inhibitory effect on CLOCK-BMAL1 and allowing a new cycle of transcription to begin ~24 hours after the last onset. A second, stabilizing loop is formed by CLOCK-BMAL1-induced transcription of retinoic acid-related orphan nuclear receptor genes – reverse-erythroblastosis virus and retinoic acid receptor-related orphan receptors (*Rora*/ β). Translated REV-ERB and ROR proteins repress and promote the transcription of

Bmal1, respectively, and reinforce the oscillatory activity of the core loop. Both spatial (nuclear and cytoplasmic localization of clock proteins) and temporal (production and degradation rate) dynamics of the circadian clockwork are mainly post-transcriptionally regulated. The approximately 24-hour periodicity is determined by the rate of clock protein degradation resulting from an interplay of various post-translational modifications, including phosphorylation (e.g., casein kinases [CKI ϵ/δ and CKII], glycogen synthase kinase 3 β [GSK3 β], and adenosine monophosphate-activated kinase [AMPK]), ubiquitination (e.g., β -TrCP1/2 and FBXL3/21), acetylation, and SUMOylation. The degradation rate is slowed by phosphatases (PP1/5), which dephosphorylate the clock components making them unavailable for degradation. In addition, the circadian clocks receive additional modulatory input regarding metabolic activity via pathways including AMPK, mammalian target of rapamycin (mTOR), and sirtuin-1 (SIRT1) signaling. B. The SCN relays its circadian entraining information to the peripheral clocks using humoral signals (e.g., cortisol and melatonin), autonomic nervous system, body temperature, and feeding-related cues. The peripheral clocks transmit back reciprocal input based on the environmental variables they are tracking, including nutrient availability, environmental temperature, physical activity, and social interaction. While the overall mechanism of the clock is conserved across both central and peripheral oscillators, the peripheral clocks differ in their tissue-specific variations of molecular architecture. Compared to the SCN, which can hold the regular circadian rhythmicity for extended periods even in absence of light, most of the peripheral oscillators lose their rhythmicity rapidly when the SCN output is arrhythmic or ablated. Together, the orchestra of circadian oscillators throughout the body produce a complex interplay of time-of-day-dependent cyclic changes that affect most functions, ranging from biochemistry to behavior and mood. Based on the following articles: [Astiz, Heyde, & Oster, 2019](#); [Gallego & Virshup, 2007](#); [Herzog & Tosini, 2001](#); [Hirano, Fu, & Ptáček, 2016](#); [Stojkovic, Wing, & Cermakian, 2014](#); [Travnickova-Bendova, Cermakian, Reppert, & Sassone-Corsi, 2002](#).

In addition to the inconspicuous circadian fluctuations in various biological markers, we humans also experience an indisputable rhythm every day: the sleep-wake cycle. Sleep is a fundamental behavioral state preserved across phylogeny, indicating that it serves an essential biological function in all animals (Anafi, Kayser, & Raizen, 2019). It can be defined as a state of behavioral inactivity that typically occurs at a species-specific time of day. According to the widely accepted two-process model of sleep regulation (Borbély, 1982), the onset of sleep is influenced by homeostatic and circadian components, Process S and Process C, respectively (Fig. 1). During the time spent awake, homeostatic sleep pressure builds up and drives the brain to fall asleep (Achermann, Dijk, Brunner, & Borbély, 1993; Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981). The homeostatic mechanisms have been systematically studied using sleep deprivation (SD), in which prolonged wakefulness increases the homeostatic pressure and the need for recovery sleep. Based on the daily rhythms and routines, homeostatic and circadian factors are commonly aligned to promote sleep towards the end of a day of wakefulness or activity. However, under high sleep pressure, the need for recovery sleep can override circadian regulation to promote sleep regardless of circadian misalignment. Conversely, circadian regulation helps one to feel alert and energetic in the morning even if they have not slept at all. (See Infobox.)

In the mammalian brain, sleep can be broadly divided into two discrete stages that exhibit distinct baseline brain activity measured by electroencephalography (EEG): rapid eye movement (REM) and

non-REM (NREM) sleep (Pace-Schott & Hobson, 2002). REM sleep consists of wake-like high-frequency, low-amplitude EEG activity, along with decreased muscle tone as measured by electromyography. It is also called paradoxical sleep owing to its close resemblance to waking EEG activity. In contrast, NREM sleep in humans is divided into three stages that are dominated by high-amplitude, synchronized, low-frequency EEG activity (0.5–4.0 Hz, delta). This slow-wave activity (SWA) is most prominent during the deepest stage (stage III), named aptly as slow-wave sleep (SWS). From the beginning of a sleep period, NREM and REM sleep emerge in alternating patterns during four to five sleep cycles that occur each night in adult humans. Typically, the first sleep cycle of the night displays a longer duration of deeper NREM sleep, whereas the period of REM sleep is shorter. In the following sleep cycles, the duration of NREM sleep gets progressively shorter while the proportion of REM sleep increases. This characteristic pattern of sleep organization varies in different species and subjects. Notably, both NREM and REM sleep are homeostatically regulated in all animals. After SD, the time spent in SWS and its intensity increases (Fig. 1). Similarly, after REM sleep deprivation, the time spent in REM sleep increases during the subsequent sleep period.

The electrophysiological rhythms of sleep are unequivocally generated by the principal computational components of the brain – neural circuits and neurons. Apart from neurons, glial cells are major contributors to the maintenance, regulation, and function of sleep. Glial cells have important roles in metabolic and energetic processes, function of the glymphatic system, regulation of immune functions, and processes

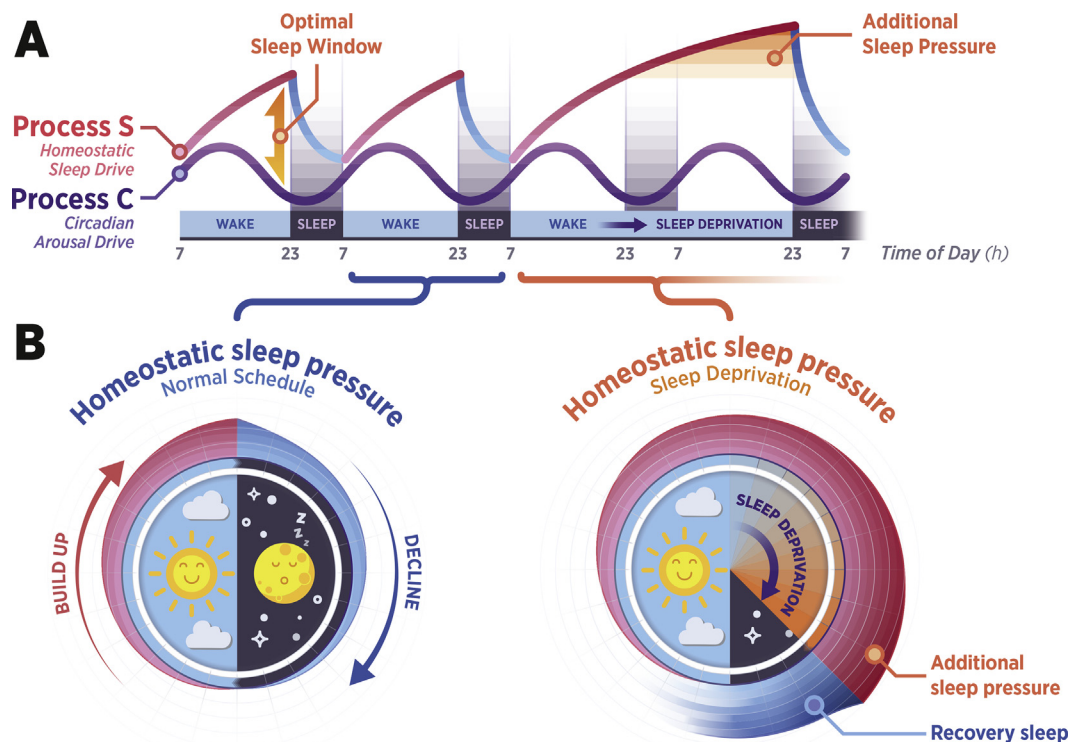


Fig. 1. Two-process model of sleep regulation. The timing of sleep and need for sleep are determined by process C and process S, respectively (Borbély, 1982). The complementary nature of the two processes is demonstrated in A, whereas B highlights the cyclic nature of homeostatic sleep drive during regular sleep-wake cycles. Process S represents sleep homeostasis, or sleep debt, which accumulates as a function of wake duration and decreases as deep sleep progresses. Process C, in contrast, exhibits oscillations with an approximately 24-hour periodicity to align the optimal level of arousal and metabolism with the surrounding environmental conditions. The timing of the cycle is synchronized to salient cues including light, nutrients, and physical and social activity. The optimal sleep window emerges when the level of sleep pressure has grown sufficient and the circadian arousal-promoting drive has subsided, usually occurring towards the end of the light period in humans. Towards morning, when enough sleep pressure has been relieved during sleep and the new cycle of process C begins to promote arousal again, waking occurs. Prolonged wake (e.g., sleep deprivation) produces increased sleep pressure and need for recovery sleep. During this extended wakefulness, subjective sleepiness declines after a night of wakefulness owing to the arousal-promoting effects of process C. While distinct, the two processes are inseparable and have complementary effects. Strong synaptic potentiation during daytime leads to increased clock entrainment and vice versa – an entrained clock during the day enables optimal excitability conditions for potentiation to occur.

related to synaptic plasticity (for a glial perspective on sleep and circadian rhythms, see [Artiushin & Sehgal, 2020](#)).

3.2. Functions of sleep

Despite great advances in the understanding of the complexity of sleep and its molecular, cellular, and functional substrates, its primary physiological functions remain unclear ([Krueger, Frank, Wisor, & Roy, 2016](#)). Sleep serves multiple functions ranging from conservation of energy, restoration of energy supplies, recovery from cellular stress, repair of cellular and DNA damage, removal of metabolic byproducts via convective cerebrospinal fluid flow, modulation of the immune system, and regulation of temperature and metabolism ([Bass & Takahashi, 2010](#); [Bellesi, Bushey, Chini, Tononi, & Cirelli, 2016](#); [Benington & Heller, 1995](#); [Inokawa et al., 2020](#); [Mackiewicz et al., 2007](#); [Refinetti & Menaker, 1992](#); [Reimund, 1994](#); [Scharf, Naidoo, Zimmerman, & Pack, 2008](#); [Xie et al., 2013](#); [Zada, Bronshtein, Lerer-Goldshtein, Garini, & Appelbaum, 2019](#)). Disturbed and insufficient sleep is associated with various disorders affecting metabolic ([Spiegel, Leproult, & Van Cauter, 1999](#)), cardiovascular ([Gangwisch et al., 2006](#)), and immunological functions ([Bryant, Trinder, & Curtis, 2004](#)); however, many of these functions may also be addressed, to a certain degree, during wakefulness or quiet rest without the requirement for the evolutionarily risky disconnection from the external environment that occurs during sleep. Thus, it can be argued that the activity that occurs in the brain during sleep-induced unconsciousness is the key to understanding the primary functions of sleep.

Remarkably, sleep duration and intensity are closely associated with brain size across species, and the depth and proportion of NREM sleep varies during different brain development stages. NREM sleep peaks during brain growth spurt and declines during adolescence ([Feinberg & Campbell, 2010](#)). It has been argued that NREM sleep during development is causally associated with brain maturation and reorganization of neuronal networks driven by synaptic elimination ([Feinberg & Campbell, 2010](#)). Indeed, the duration of NREM sleep declines with age as the sleep generally becomes more fragmented and circadian rhythmicity is reduced ([Fogel et al., 2012](#)). Moreover, sleep serves as a suitable period for the regulation of synaptic strength, memory consolidation, and learning ([Stickgold, 2005](#)). Increased memory retention is widely attributed to the function of sleep, as it markedly enhances both memory encoding and consolidation ([Walker & Stickgold, 2006](#)). Adequate sleep before memory formation, and conversely, sufficient sleep after it, support information storage in long-term memory ([Diekelmann & Born, 2010](#); [Mander, Santhanam, Saletin, & Walker, 2011](#); [Walker, 2009](#)). In contrast, disturbed and insufficient sleep is associated with the impairment of multiple cognitive domains ([Durmer & Dinges, 2005](#); [Van Dongen, Maislin, Mullington, & Dinges, 2003](#)) and susceptibility to psychiatric disorders such as major depression ([Benca, 1992](#); [Nutt, Wilson, & Paterson, 2008](#); [Ohayon & Roth, 2003](#); [Riemann, Berger, & Voderholzer, 2001](#); [Tsuno, Besset, & Ritchie, 2005](#)) (see Chapter 3.3). However, there is controversy regarding how many beneficial effects sleep may have and what neurobiological functions the different stages of sleep may promote. Although it is commonly accepted that neural plasticity occurs both during wakefulness and sleep, the overall contribution to synaptic change and synaptic plasticity remains unclear.

It has been proposed that neuroplastic changes initiated during the encoding of waking experience trigger transient changes and prime circuits and synapses to undergo further processing in sleep ([Seibt & Frank, 2019](#)). For example, in the hippocampus, firing sequences corresponding to particular experienced events during wakefulness can be reactivated during SWS and primed synapses may undergo protein synthesis-dependent changes that support structural modifications required for long-term information storage. Sleep may also serve a role in the active system consolidation of memory by redistributing newly encoded memory engrams, for example, from the hippocampus to the cortex ([Born & Wilhelm, 2012](#)). Moreover, recent studies suggest that dendritic spines in layer V pyramidal neurons of the motor cortex are

influenced by both REM and NREM sleep. In particular, REM sleep is associated with the selective pruning and maintenance of new dendritic spines following motor learning ([Li, Ma, Yang, & Gan, 2017](#)), whereas the reactivation of neurons following motor learning in NREM sleep is involved in the facilitation of spine formation ([Yang et al., 2014](#)). Further research is required to thoroughly investigate how different sleep stages ultimately affect spine dynamics; nevertheless the above-mentioned studies highlight the important connection between sleep and the regulation of synaptic function. To make things more complicated, mechanisms of plasticity during wake and sleep may vary between areas of the brain, subtypes of neurons, and types of memory and learning. Many of the proposed hypotheses are not mutually exclusive, and ultimately many different processes likely contribute to the synaptic changes associated with sleep.

Many hypotheses examining the role of sleep in memory consolidation and facilitation of synaptic plasticity focus on SWS and SWA – also regarded as markers of sleep intensity. The amount and intensity of sleep SWA are strongly correlated with cortical activity during the previous wakeful period. This is particularly demonstrated by the pronounced increase in SWA during recovery sleep after SD ([Huber, Deboer, & Tobler, 2000](#)) ([Fig. 1](#)). The connection between cortical activity and SWA can also be observed on the level of cortical microcircuits ([Tononi & Cirelli, 2014](#)). This is exemplified by studies utilizing a hand motor coordination task or arm immobilization, which are mirrored by increased and decreased SWA, respectively, in the corresponding cortical areas during sleep ([Huber et al., 2006](#)). Skilled reaching tasks in rats and repetitive transcranial magnetic stimulation and somatosensory stimulation in humans also lead to increased SWA during the subsequent sleep episode ([Hanlon, Faraguna, Vyazovskiy, Tononi, & Cirelli, 2009](#); [Huber et al., 2007](#); [Kattler, Dijk, & Borbély, 1994](#)). An increase in local SWA during sleep may reflect increased synaptic potentiation elicited by the administered stimulus or task ([Tononi & Cirelli, 2014](#)).

The connection between synaptic potentiation and SWA is one of the features discussed in the synaptic homeostasis hypothesis (SHY), which proposes that sleep functions to reestablish synaptic homeostasis after a period of wake and learning ([Tononi & Cirelli, 2014](#)) ([Fig. 2](#)). A key argument of SHY is that there is an observable net increase and decrease in synaptic potentiation during wake and sleep, respectively ([Tononi & Cirelli, 2003](#); [Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008](#)). The SHY suggests that sleep offers an ideal opportunity for the downregulation or renormalization of synaptic strength owing to the effective sensory disconnection of the brain from the external environment ([Tononi & Cirelli, 2012](#)). During this process, neurons may sample their inputs without external influence and effectively downregulate synaptic weights. As argued in the SHY, this process is crucial for maintaining brain functionality, because a continuous increase in synaptic strength across neurons cannot be sustained for long. Stronger synapses consume more space, energy, and cellular resources while ultimately saturating the capacity for learning and information processing. Moreover, the SHY suggests that the number and strength of synaptic connections are proportional to the amplitude and slope of SWA during sleep, and that sleep SWA may be causally involved in synaptic homeostasis. This has been addressed in computer simulations, where higher synaptic strength, neuronal activity, and synchrony result in increased SWA, which produces more synaptic depression ([Esser, Hill, & Tononi, 2007](#); [Olcese, Esser, & Tononi, 2010](#)). Once synaptic strength is decreased, the amount and intensity of SWA decline, providing a self-limiting mechanism. Indeed, numerous experiments have shown that the markers associated with synaptic potentiation decline during sleep in a non-linear pattern similar to reduction in SWA during sleep ([Riedner et al., 2007](#); [Tononi & Cirelli, 2020](#); [Vyazovskiy et al., 2009](#)). These markers include synapse size ([Cirelli & Tononi, 2020](#); [de Vivo et al., 2017](#)), AMPAR expression ([Diering et al., 2017](#); [Vyazovskiy et al., 2008](#)), evoked responses and field excitatory postsynaptic potentials ([Huber et al., 2013](#); [Norimoto et al., 2018](#); [Vyazovskiy et al., 2008](#)). Molecular mechanisms involved in the down-selection of excitatory

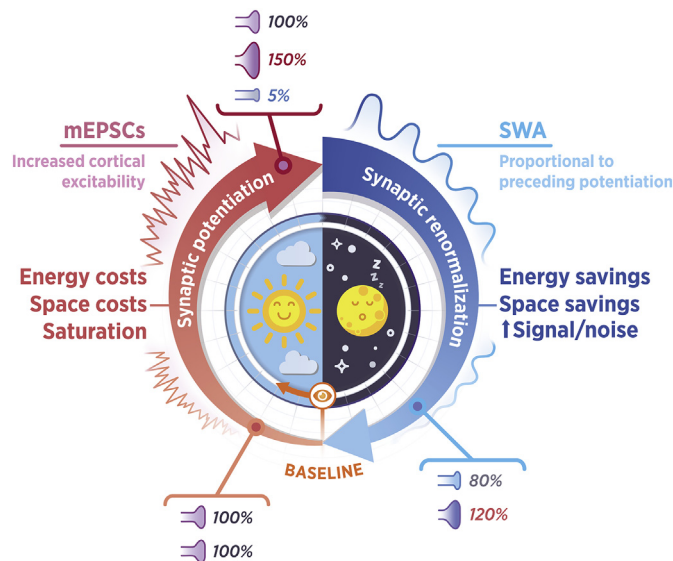


Fig. 2. Sleep restores synaptic and cellular homeostasis. Synaptic potentiation and synaptogenesis during wakefulness are considerably costly in terms of resources and space, leading to saturation of neuronal plasticity. To counteract this phenomenon, the brain undergoes a systematic renormalization of synaptic strength during sleep (Tononi & Cirelli, 2003; Tononi & Cirelli, 2014), which allows the brain to restore synaptic plasticity, consolidate learning, and prevent the overflow of metabolic costs associated with continuous wakefulness. Synaptic potentiation increases as a nonlinear function of time spent awake, as evidenced by the wake-time-dependent increase in the amplitude and frequency of miniature excitatory postsynaptic currents (mEPSCs). Synaptic renormalization during sleep follows homeostatic regulation; the magnitude and localization of slow-wave electroencephalographic activity (SWA) during nighttime reflect the intensity and localization of the preceding potentiation. By the end of the day, certain synapses gain strength according to their activity and new connections are formed. During sleep, the synapses may be downregulated in proportion to their strength. In the image, the transition to wake from sleep (baseline) is denoted using orange eye and arrow. The numerical values on the outer edge represent a cycle of potentiation in a set of neurons during a sleep-wake cycle.

synapses during sleep include, for example, Homer1a, group I metabotropic glutamate receptors (Diering et al., 2017; Hu et al., 2010), and GSK3 β (Tononi & Cirelli, 2020).

3.3. Association between depression and disturbances in sleep and circadian regulation

Major depression is known to be associated with abnormalities in circadian regulation and sleep (Benca, 1992; Nutt et al., 2008; Ohayon & Roth, 2003; Van Cauter & Turek, 1986). Up to 90% of depressed patients report impaired sleep quality and typically experience prolonged sleep latency, fragmented sleep, and early morning awakenings (Riemann et al., 2001; Tsuno et al., 2005). The subjective reports of altered sleep quality are accompanied by electrophysiological findings of altered sleep architecture affecting both NREM and REM sleep. The most common finding is a reduction in the amount of SWS (Borbély & Wirz-Justice, 1982; Tsuno et al., 2005). In addition, depressed patients display a shorter latency to first REM sleep episode, and the intensity of REM sleep is increased (Benca et al., 1997); however, these changes are not specific to affective disorders (Riemann et al., 2020).

Many patients with depression show a diurnal pattern of mood variation, i.e. a low mood during the morning, which is alleviated throughout time spent wake towards the evening (Riemann et al., 2020). Moreover, depression is often modulated by seasonal change, perhaps due to the changing amount of daylight. Clinical studies indicate a correlation between the degree of desynchronization in circadian rhythms and the severity of depression (Hasler, Buysse, Kupfer, & Germain, 2010). On the other hand, rhythm disrupting conditions, such as shift work or jet lag, may worsen depressive mood (Kalmbach, Pillai, Cheng, Arnedt, & Drake, 2015). In experiments on rodents with the

central pacemaker rendered either completely aperiodic (Landgraf et al., 2016), internally desynchronized (forced desynchronization (Ben-Hamo et al., 2016)), or under constant light schedule (Ohta, Yamazaki, & McMahon, 2005), phases of temperature, locomotion, and sleep-wake cycles became decoupled from one another. The decoupling leads to symptoms and changes characteristic for a depression-like state: anhedonia, sexual dysfunction, behavioral despair, reduction of dendritic complexity in the hippocampus and mPFC, and altered corticosterone production (Ben-Hamo et al., 2016; Buijs, Kalsbeek, van der Woude, van Heerikhuizen, & Shinn, 1993; Karatsoreos, Bhagat, Bloss, Morrison, & McEwen, 2011; Phillips, Savenkova, & Karatsoreos, 2015; Wotus et al., 2013). Indeed, circadian patterns of gene expression in the human brain have been shown to be markedly abnormal across six brain areas in MDD (Li et al., 2013). It could be therefore argued that depressed individuals may have dysregulated circadian activity, which could stem from e.g. the central pacemaker or direct light-dependent regulation of individual brain areas. For an example of the latter, lateral habenula is directly connected with SCN – alongside with dopaminergic and serotonergic systems – and may display both intrinsic oscillations and direct responses to retinal light (Langel et al., 2018; Mendoza, 2017; Riemann et al., 2020).

Effects of conventional antidepressants on sleep have been studied since the 1960s, however, specific alterations that would explain antidepressant actions have not been found. Generally, monoaminergic antidepressants tend to normalize sleep architecture of depressed patients by reducing the amount of REM sleep and increasing REM latency (Sandor & Shapiro, 1994). The effects of these drugs on sleep EEG correlate with clinical response and appear to be persistent during long-term treatment, suggesting that the normalization of sleep architecture might play a role in the therapeutic action of these drugs (Ehlers, Havstad, & Kupfer, 1996; Kupfer et al., 1994). Moreover, normalization of the circadian rhythms commonly emerges alongside with improvement in depressive symptoms (Bunney et al., 2015; Bunney & Bunney, 2012). Perhaps the most fascinating link between sleep, circadian rhythm, and depression comes from clinical observations with SD. In healthy controls, SD can increase feelings of dysphoria (Gerner, Post, Gillin, & Bunney, 1979), while in depressed patients SD can induce remarkably rapid amelioration of symptoms (Pflug & Tolle, 1971; Wirz-Justice & Van den Hoofdakker, 1999). Today, SD is used in an inpatient setting in some countries, with 38.7% of psychiatric hospitals from German speaking countries report having treated patients with SD during the last 12 months (Winkler et al., 2019). Published studies document that even up to 50–60% of patients with severe depression respond to SD, however, the antidepressant effects are highly transient and symptoms typically reappear after the next sleep episode (Boland et al., 2017). Intriguingly, the clinical improvements from SD have been reported to stabilize and better preserve when patients are treated with lithium (Baxter et al., 1986; Szuba et al., 1994), magnetic stimulation (Eichhammer et al., 2002), or phase advance (Echizenya, Suda, Takeshima, Inomata, & Shimizu, 2013; Riemann et al., 1999; Wu et al., 2009) and bright light therapies (Echizenya et al., 2013; Martiny et al., 2013; Neumeister et al., 1996). Many unresolved questions remain regarding the underlying mechanisms of the antidepressant effects of SD, but LTP-like synaptic plasticity and transcriptional regulation of circadian genes have been suggested to be involved (Orozco-Solis et al., 2017; Wolf et al., 2016). This logically brings us towards the discussion of how sleep and circadian regulation may be related with the antidepressant effects of ketamine and other rapid-acting antidepressants.

4. Rapid-acting antidepressants: shifting the focus towards sleep and circadian regulation

4.1. Rapid antidepressant effects and sleep homeostasis

How can a single dose of a short-acting drug like ketamine achieve such rapid, yet long lasting effects? From the perspective of traditional

pharmacology, these effects must be born out of the engagement of target receptors, i.e. blockade of NMDARs, and subsequent molecular alterations specifically regulated by the ketamine and/or some of its metabolites. Interestingly, the effects of ketamine are closely connected to the mechanisms of sleep regulation, as overviewed in Chapter 2, namely through facilitation of glutamatergic neurotransmission by the preferential blockade of NMDARs on GABAergic interneurons. This is thought to lead into disinhibition of pyramidal neurons, and increased excitation and BDNF release, ultimately resulting in the activation of cellular signaling cascades that facilitate synaptic plasticity and synaptogenesis. However, approaching this issue from a more neurobiological perspective may offer further insights into the actions rapid-acting antidepressants. Here we focus on the effects of ketamine which extend beyond the acute pharmacological effects, such as neurobiological adaptations that emerge in response to ketamine treatment and its withdrawal. In particular, we review recent studies and hypotheses which connect the effects of ketamine to physiological mechanisms of sleep and circadian regulation.

Accumulating data from clinical trials and experts suggests that the effects of ketamine can be very rapid, with amelioration of depressive symptoms becoming evident already during the infusion (Kishimoto et al., 2016; Murrough et al., 2013; Zarate Jr et al., 2006). During this period of immediate pharmacological action, ketamine increases glutamate release, energy metabolism, and the secretion of BDNF along with the activation of multiple molecular pathways that are thought to contribute to increased protein synthesis and synaptic plasticity. Patients with robust improvements in depressive symptoms after ketamine infusion exhibit increased cortical excitability as measured by stimulus-evoked somatosensory responses (Nugent et al., 2019). Moreover, several studies have demonstrated increases in gamma power both acutely and several hours after ketamine treatment in depressed patients, with some of the studies also showing an association between gamma power and treatment response (for a thorough review see, Gilbert & Zarate, 2020). In one study, subjects who had low baseline gamma power and experienced larger increases in response to ketamine showed better antidepressant responses (Nugent, Wills, et al., 2019). While the dissociative and psychotomimetic effects of ketamine have also been connected to the acute increase in gamma oscillations, the sustained and elevated gamma power post-ketamine has been suggested to be a potential biomarker for ketamine-induced synaptic potentiation (Gilbert & Zarate, 2020). These and other studies suggest that ketamine-induced synaptic potentiation and modulation of network activity may be crucial for the rapid antidepressant effects to develop (Gilbert & Zarate, 2020). This idea is supported by a recent study in an animal model of chronic stress, where ketamine rapidly restored coordinated activity in cortical neuronal ensembles and normalized behavior (Moda-Sava et al., 2019). Notably, several clinical studies have reported that the most robust action on depressed mood is often observed on the following day of the ketamine treatment, i.e., after a night of sleep (Coyle & Laws, 2015). As previously discussed, arguably the largest physiological change in the brain takes place from wakefulness to sleep, yet sleep is rarely considered in the study of rapid antidepressant effects. Intriguingly, the seminal work of Feinberg and Campbell (Campbell & Feinberg, 1996; Feinberg & Campbell, 1993) demonstrated already decades ago that subanesthetic administration of ketamine or dizocilpine (another NMDAR antagonist) during wake increases SWA (or delta EEG intensity) during subsequent NREM sleep in rats. Already in these early studies, the authors pointed out a possible connection between the effects of ketamine, glutamatergic neurotransmission, and the regulation of sleep homeostasis. The link between the effects of ketamine and sleep homeostasis is strengthened by a clinical study, where ketamine increased total sleep time, SWS and REM sleep in treatment-resistant depressed patients (Duncan et al., 2013). Moreover, the increases in the amount of SWA the night following ketamine treatment were correlated with mood improvement (Duncan, Sarasso, et al., 2013). In particular, the group of responders showed significant

correlations between SWA, slow wave amplitude, and increases in plasma BDNF (samples collected 230 minutes after the infusion). Since both increases in sleep SWA and levels of BDNF are functionally related to synaptic strength, the results support the idea that a net gain of synaptic potentiation takes place during treatment, which results in the increased emergence of SWA during the subsequent sleep period (Duncan, Sarasso, et al., 2013). In another study, the baseline delta-sleep ratio (DSR; the ratio of SWA between the first two NREM sleep episodes) of depressed patients was found to predict the antidepressant response to ketamine on the day following administration, i.e. after a night of sleep (Duncan, Selter, Brutsche, Sarasso, & Zarate, 2013). A low DSR score predicted better treatment response, whereas high score predicted poor response. As discussed by the authors of the study, these results suggest that ketamine responders exhibit dysregulated synaptic homeostasis during sleep, which may be positively affected by the treatment.

The release of BDNF and facilitation of SWA may be related to cortical excitation induced by subanesthetic ketamine because neuronal utilization during wake by itself has been shown to be sufficient to upregulate BDNF levels and induce rebound SWA in rodents (Huber, Tononi, & Cirelli, 2007). Indeed, other rapid-acting treatments of depression affecting cortical excitation during wake, such as SD (Giese et al., 2014) and electroconvulsive therapy (Rocha et al., 2016), also rapidly increase the circulating BDNF levels and SWA during the subsequent sleep period in depressed patients (Göder et al., 2016). The close association between activity-dependent release of BDNF and synaptic homeostasis is further supported by animal studies in which intracortical BDNF administration increased subsequent sleep SWA in the injected hemisphere (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008). In this study, the infusion of either BDNF-blocking antibodies or K252a (a receptor tyrosine kinase inhibitor commonly used to reduce TrkB activity) led to reduced SWA response. Notably, BDNF or the blockers did not significantly affect sleep duration, suggesting that cortical BDNF infusion increases synaptic strength, which contributes to the generation of SWA (Faraguna et al., 2008). Moreover, other studies have shown that mice with disrupted activity-dependent *Bdnf* promoter IV display a decrease in SWA during NREM sleep (Hill et al., 2016). These results are also supported by human studies in which subjects with the Val66Met BDNF polymorphism – which impairs activity-dependent BDNF secretion – show lower SWS intensity after SD than those with the Val66Val BDNF polymorphism (Bachmann et al., 2012).

It is well established that BDNF is a key mediator of synaptic plasticity and strength in the adult brain (Park & Poo, 2013), and SWA may represent the synaptic strength of cortical circuits. As proposed by the SHY, increased synaptic potentiation is observed as increased SWA during subsequent NREM sleep, when the renormalization of synaptic strength occurs. In this context, it remains possible that ketamine, and several other excitatory treatments, are capable of rapidly engaging cortical microcircuits, thus increasing their activity and synaptic strength. This increase in synaptic strength is reflected in the increased amount of SWA observed during subsequent sleep period. The SHY proposes that the global renormalization of synaptic strength occurs during SWS, whereas synapses that were particularly active and potentiated during preceding wakefulness may be protected, to a certain extent, from this process. The underlying mechanisms remain speculative at this time, but the proposed framework may be highly relevant for understanding learning and memory consolidation and exploring how rapid antidepressant effects emerge and, especially, sustain over time.

In the recent years, several new hypotheses have approached rapid and sustained antidepressant effects through the function of sleep. A recently formulated hypothesis of encoding, consolidation and renormalization in depression (ENCORE-D) views rapid antidepressant effects by separating the rapid onset and realization of the sustained action into three consecutive phases (Rantamäki & Kohtala, 2020) (Fig. 3). The first phase, encoding, constitutes events that occur under the acute pharmacological effects of a drug (i.e. engagement of target receptors).

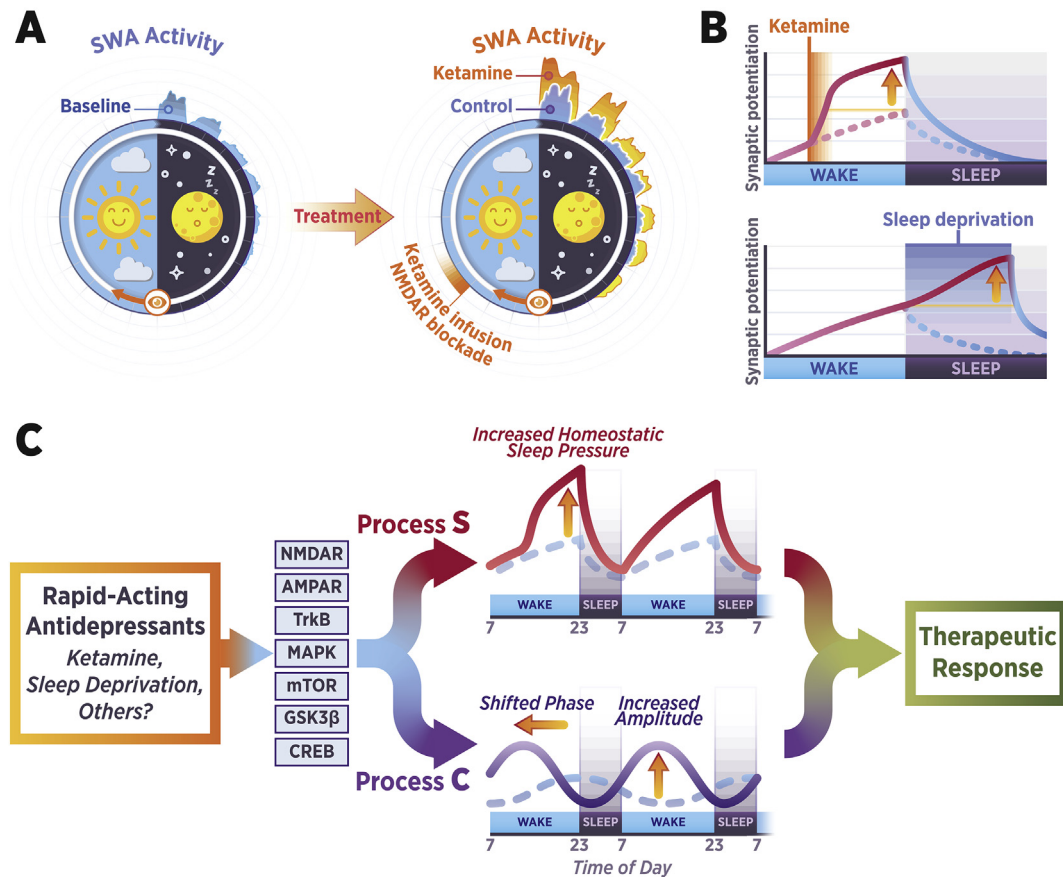


Fig. 3. Chronotherapeutic features are integral components of rapid-acting antidepressants. A. Subanesthetic ketamine transiently evokes glutamatergic neurotransmission in the cortex during peak pharmacological effects, for example, through inhibition of *N*-methyl-D-aspartate receptors (NMDAR) on GABAergic interneurons and facilitation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)-mediated neurotransmission. Excitatory neurotransmission is also facilitated during sleep deprivation. Increased excitation results in synaptic potentiation, which is then reflected in more prominent slow wave activity (SWA) during the subsequent sleep episode. According to the encoding, consolidation and renormalization in depression (ENCORE-D) hypothesis (Rantamäki & Kohtala, 2020), this phenomenon is important for sustaining the antidepressant effects of ketamine. B. A hypothesis by Wolf et al. (2016) suggests that depression (dashed line) is characterized by a deficiency in synaptic plasticity and an inability of synapses to reach an optimal zone of potentiation where long-term potentiation can be induced. Sleep deprivation and, possibly, ketamine can therefore be utilized to increase cortical excitability and synaptic potentiation, compensating for the impaired associative plasticity of the depressed brain. C. Molecular mechanisms associated with the therapeutic effects of rapid-acting antidepressants are also principal components of circadian clockwork and intrinsic brain excitability. Various pharmacological and non-pharmacological treatments of depression produce similar changes in the expression of proteins associated with process S (synaptic potentiation), and/or process C (timing and amplitude of circadian clock output). TrkB, tropomyosin-related kinase B; MAPK, mitogen-activated protein kinase (also known as extracellular signal-regulated kinase or ERK); mTOR, mammalian target of rapamycin; GSK3 β , glycogen synthase kinase β ; CREB, cAMP response element-binding protein.

The hypothesis proposes that ketamine's ability to transiently excite cortical neurocircuits – by facilitating glutamatergic activity – alters their computational properties and patterns of connectivity. This rapidly switches network functionality and normalizes depressogenic cognitive processes while facilitating the encoding of healthy network activity and accrual of synaptic strength – processes that may be dysregulated in, for example, chronic depressive rumination – for the remainder of the day. Hypothetically, the gradual cessation of the acute pharmacological effects triggers a second phase that involves the homeostatic emergence of SWA in activated neurocircuits while awake, which coincides with molecular signaling events and synthesis of proteins involved in the consolidation of synaptic plasticity. Such phenomenon is also observed in experiments with nitrous oxide (“laughing gas”), another NMDAR antagonist and a putative rapid-acting antidepressant (Nagele et al., 2015), which evokes cortical SWA specifically upon drug withdrawal accompanied by enhanced TrkB, GSK3 β and p70S6K (an effector of mTOR) signaling (Kohtala et al., 2019). Moreover, subanesthetic ketamine and various other treatments that possess rapid antidepressant potential, such as ECT, flurothyl, and theta burst stimulation, increase SWA after the acute pharmacological (or physiological) effects have dissipated (Assenza, Pellegrino, Tombini, Di Pino, & Di Lazzaro, 2015; Kohtala, Theilmann, Rosenholm, Penna, et al.,

2019; Sackeim et al., 1996). Finally, the third phase occurs during subsequent SWS, a period during which, according to the SHY, cortical neurocircuits undergo synaptic renormalization (Tononi & Cirelli, 2014), challenged by increased synaptic strength and synaptogenesis (Li et al., 2010). ENCORE-D suggests that this phenomenon gives rise to more persistent changes in circuit activity, by allowing ketamine-induced synaptic changes to be maintained, whereas the processes attributed to the maintenance of depressive cognitive processing may be downregulated (Rantamäki & Kohtala, 2020). These effects culminate the following day, when the most robust antidepressant effects become evident along with normalized patterns of global functional connectivity (Abdallah et al., 2017). Most importantly, ENCORE-D suggests that the core of ketamine's effects lies in its ability to transiently alter neuronal activity in cortical circuits, which recruits the activity of fundamental homeostatic processes during SWS, ultimately altering the patterns of neural activity and flow of implicit cognitive processes beneficial for maintaining thought patterns free of depression (Rantamäki & Kohtala, 2020). Furthermore, the principles of the hypothesis can be applied to examine both the pathophysiology leading to depression (i.e. aberrant accrual and maintenance of synaptic strength in depressogenic networks) and the relapse of depressive symptoms over time (i.e. several wake-sleep cycles). Although ENCORE-D remains

highly speculative and requires rigorous experimental proof, it effectively proposes a novel framework for examining rapid and sustained antidepressant effects from the perspective of sleep.

Another hypothesis, the synaptic plasticity model of SD as a treatment of depression, similarly focuses on synaptic homeostasis and sleep/wake-dependent shifts in synaptic plasticity particularly influenced by SD (Wolf et al., 2016). In this hypothesis, depression is characterized by deficient synaptic plasticity and the inability of synapses to reach an optimal zone for LTP inducibility. Studies demonstrating diminished hippocampal LTP inducibility in animal models of depression (Alfarez et al., 2003) and a decrease in LTP-like cortical plasticity in patients suffering from depression (Normann et al., 2007; Player et al., 2013) provide support for the general idea. In particular, the hypothesis proposes that SD extends the period when cortical neurons may increase their synaptic strength or excitability, which compensates for the attenuated associative plasticity in depression and leads to the amelioration of depressive symptoms. Notably, rodent studies have shown that wakefulness increases the slope and amplitude of evoked cortical responses, whereas a decrease is observed after sleep (Vyazovskiy et al., 2008). Moreover, the levels of extrasynaptic glutamate (Dash, Douglas, Vyazovskiy, Cirelli, & Tononi, 2009), frequency and amplitude of miniature excitatory postsynaptic currents, and mean firing rate and synchronization of cortical neurons increase after prolonged wakefulness (Liu, Faraguna, Cirelli, Tononi, & Gao, 2010). Human studies have also demonstrated an increase in cortical excitability during wakefulness (Huber et al., 2013). The notion that depressive symptoms are associated with dysregulated synaptic strength is supported by indirect evidence from a study where cortical excitability was measured as a proxy of synaptic strength in patients with bipolar depression (Canali et al., 2014). The study demonstrated that changes in cortical excitability parallel and predict antidepressant responses to SD and light therapy. Together, these and other findings provide support for increases in cortical synaptic strength in association with time spent awake. In its current form, the model by Wolf et al. (2016) provides an intriguing perspective on how SD may act through modulating the mechanisms of synaptic plasticity and sleep to ultimately influence depressive symptoms. This framework could also potentially be applied to examine excitatory drugs such as ketamine, which also affects cortical excitability (Rantamäki & Kohtala, 2020).

4.2. Antidepressant effects of ketamine and circadian regulation

Emerging views highlight the role of circadian dysregulation in the pathophysiology of depression and regulation of mood (see Chapter 3.3.). Indeed, traditional antidepressants may influence circadian mechanisms and modulate sleep structure. It appears reasonable that the effects of ketamine may also recruit circadian mechanisms, which participate in the rapid and sustained recovery of depressive symptoms. Although the effects of ketamine on circadian regulation are not fully elucidated, several studies suggest that many of the molecular targets regulated by ketamine are also closely associated with modulation of circadian systems.

Preclinical studies indicate that both SD and ketamine influence the function of the circadian molecular components, leading to altered clock gene transcriptional output levels (Bellet, Vawter, Bunney, Bunney, & Sassone-Corsi, 2011; Bunney et al., 2015; Orozco-Solis et al., 2017; Wisor et al., 2008) (Fig. 3), but the precise underlying mechanisms can be only speculated at this point. The intracellular pathways leading from entraining cue-induced neuronal activation to gene expression are originally initiated by neuronal activity triggering Ca^{2+} -regulated protein kinases (Golombek & Rosenstein, 2010; Meijer & Schwartz, 2003). The Ca^{2+} signaling is mobilized by various mechanisms including NMDAR activation, voltage-gated calcium channel opening, release from intracellular storage, and G protein-coupled receptor-mediated signaling (West et al., 2001). A recent study shows that ketamine triggers a gradual emergence of synaptic calcium transients in pyramidal

neurons within the PFC (Ali et al., 2020). Experimental evidence suggests that, downstream of Ca^{2+} influx, ERK1/2, GSK3 β , protein kinases A and G (PKA and PKG), and Ca^{2+} -calmodulin-dependent protein kinases play a key role in the modulation of clock phase shifts in rodent SCN (Alessandro, Golombek, & Chiesa, 2019; Iitaka, Miyazaki, Akaike, & Ishida, 2005). Eventually, various excitatory stimuli that are sufficient to synchronize the circadian clock lead to the phosphorylation of CREB at the transcriptional activation site Ser¹³³, initiating expression of IEGs and clock-controlled genes (Ginty et al., 1993; Hastings et al., 1997; Lee et al., 2010; Lonze & Ginty, 2002). Thus, the CREB pathway serves as a crucial point of convergence for various cues of photic and non-photic origin in the synchronization of circadian rhythmicity. Notably, the acute pharmacological effects of ketamine also converge on the same pathways, resulting in the regulation of core components of the mammalian circadian clock (Beurel et al., 2011; Beurel, Grieco, Amadei, Downey, & Jope, 2016; Kohtala, Theilmann, Rosenholm, Müller, et al., 2019; Ma et al., 2017; Réus et al., 2016; Wang et al., 2020; Wray, Schappi, Singh, Senese, & Rasenick, 2019); INFOBOX). Certain aspects of the potential impact of ketamine on circadian rhythms can also be examined through its effects on energy expenditure and behavior (increase in locomotor activity; see, e.g., Campbell & Feinberg, 1996; Feinberg & Campbell, 1993), both strong non-photic entraining cues for circadian rhythm. Indeed, a common feature of non-photic stimuli is their ability to arouse and increase physical activity (and thereby energy consumption) (Hastings, Duffield, Smith, Maywood, & Ebling, 1998; Mrosovsky, 1996). Notably, the effects of arousal are most pronounced at the end of the inactive phase (Hastings et al., 1998).

At this stage, it remains unclear at what level subanesthetic ketamine may affect circadian regulation, and whether these effects are mediated through a global increase in cortical activity or more specific effects on individual brain areas and circuits. A model by Duncan et al. (2017) suggests that the effects of ketamine may be explained through alterations in both the homeostatic (S) and circadian (C) components of sleep. Specifically, this hypothesis proposes that diminished interactions between these mechanisms promote depressed mood. Treatment with ketamine increases plasticity, SWS, and sleep quality while altering circadian timing and output. By increasing the circadian amplitude and shifting its phase, ketamine restores the circadian misalignments present in depressed patients. Indeed, human studies have reported an association between the antidepressant effects of ketamine and circadian timekeeping (Duncan et al., 2017; Duncan et al., 2018). Previous studies have also reported a correlation between ketamine-induced changes in BDNF levels, SWS, sleep quality, and concomitant mood changes in treatment-resistant depression (Duncan, Sarasso, et al., 2013; Duncan & Zarate, 2013). Duncan et al. (2017) discuss various potential effects of ketamine's on circadian timekeeping. For example, ketamine may affect the timekeeping of the central clock or alter its synchronization to external light cycles. Its effects may also stem from its impact on the expression of non-central clock genes. Additionally, it should be noted that processes S and C complement each other (Deboer, 2018), and the effects of ketamine cannot be isolated to either individually. Sufficient neuronal activity alters circadian output by entraining the circadian clock, and conversely, the threshold for synaptic potentiation occurring in response to neuronal activity is lower during proper circadian time.

The lateral habenula (LHb) is one of the brain areas that are connected with the SCN and could be potential candidates for circadian effects induced by ketamine. The LHb appears to function as an individual circadian oscillator in the central nervous system (Mendoza, 2017). Hyperactivity of the LHb has been recently associated with the pathophysiology of depression (Aizawa, Cui, Tanaka, & Okamoto, 2013; Hu, Cui, & Yang, 2020; Lecca, Mey, & Mameli, 2014; Li et al., 2011). In particular, it exhibits inhibitory control over connecting dopaminergic, noradrenergic, and serotonergic areas. Increased activity of the neurons in the LHb may, therefore, promote stronger inhibitory control over these areas and have a negative influence on mood regulation. Notably, a recent rodent study demonstrated that depressive-like animals show

increased burst activity in LHB neurons, which can be reversed using ketamine (Yang et al., 2018). In line with these results, the downregulation of LHB reduces default mode network connectivity in rats (Clemm von Hohenberg et al., 2018). Default mode network hyperactivity is a common feature replicated in several neuroimaging studies of depressed patients (Zhou et al., 2020).

In addition to the effects of ketamine on circadian mechanisms, circadian rhythms and the time of drug administration may also directly affect the pharmacology of ketamine. The ability of ketamine to regulate specific molecular, cellular, and functional targets involved in antidepressant effects may differ depending on the phase of the circadian cycle. Indeed, the time of drug administration has significant effects on the efficacy of various drugs; however, the impact of the timing of drug delivery has generally received very little attention in medicine (Ruben, Smith, FitzGerald, & Hogenesch, 2019). Circadian oscillations in the physiological functions of the body result in considerable diurnal variations in the expression of drug targets and drug metabolizing enzymes (Levi & Schibler, 2007). The brain is no exception; the synaptic function undergoes a distinct circadian variation (Nakatsuka & Natsume, 2014; Pennartz, Hamstra, & Geurtsen, 2001; Wang et al., 2012). A recent study demonstrated circadian rhythmicity in approximately 70 % of synaptic transcripts from mouse forebrain, highlighting the role of neuronal circadian clocks in the anticipation of environmental cycles (Noya et al., 2019). The transcriptional peaks of genes associated with synaptic transmission were observed before the transition to wakefulness, whereas those of genes associated with intracellular signaling, translation, cell morphology, and metabolism, were observed before the transition to sleep. The synaptic transcriptional machinery works resiliently according to the circadian clock rhythm. When subjected to SD, the circadian oscillations in mRNA expression remain unaltered or are reduced only slightly. In contrast, the circadian rhythms of protein abundance and phosphorylation status are considerably more dependent on the quality and duration of the preceding wake or sleep period (Brüning et al., 2019; Noya et al., 2019). Thus, gene transcription is heavily controlled by circadian components, whereas the post-translational modifications enable rapid changes in the system on the basis of environmental changes. The availability of central receptor targets of ketamine, such as NMDAR and AMPAR subunit mRNAs, also undergoes circadian periodicity within the SCN (Chambille, 1999; Ishida, Matsui, Mitsui, & Mishina, 1994). This fluctuation may partially explain the circadian variations in the hypnotic efficacy of ketamine in rodents (Rebuelto, Ambros, Montoya, & Bonafine, 2002; Rebuelto, Ambros, Waxman, & Montoya, 2004; Sato et al., 2004). Moreover, total protein expression and phosphorylation levels of the molecular determinants of synaptic plasticity, such as calcium-calmodulin dependent protein kinase II, GSK3 β , and glutamate receptor 1, are differentially regulated during sleep and wake in the rat brain (Vyazovskiy et al., 2008). GSK3 β (Besing et al., 2017) and ERK1/2 activity also undergo circadian regulation (Coogan & Piggins, 2004; Obrietan, Impey, & Storm, 1998).

Finally, basic pharmacokinetic properties of ketamine may also be affected by circadian fluctuations and the wake-sleep cycle. The distribution of drugs affecting the central nervous system is generally influenced by the diurnal variations in the blood-brain barrier permeability (Cuddapah, Zhang, & Sehgal, 2019). Notably, sleep loss dramatically increases blood-brain barrier permeability (He et al., 2014). Considering that ketamine undergoes hepatic metabolism (Mössner, Schmitz, Theurillat, Thormann, & Mevissen, 2011), a process susceptible to circadian rhythmicity, and that its HNK metabolites potentially have antidepressant effects, it is even more likely that the therapeutic effects of ketamine are affected by the time of administration. For example, more HNK is produced when ketamine is administered during the active phase of the animal (Martinez-Lozano Sinues, Kohler, Brown, Zenobi, & Dallmann, 2017).

4.3. Unforeseen consequences

As outlined in the previous chapters, many of the mechanisms involved in the antidepressant effects of ketamine are also interconnected with physiological circadian rhythmicity and/or the sleep-wake cycle. These intrinsic oscillations occur at all levels ranging from molecular to cellular, and on a scale ranging from electrophysiological to ultrastructural – ultimately also modulating cognition, mood, and behavior. They span a wide range of different states and associated phenotypes, from the active wakefulness of a well-rested brain to the heavily fatigued and dysfunctional brain at the end of a long period of wakefulness. Furthermore, the brain does not cease to be inactive once asleep but instead cycles through periods of NREM and REM sleep in addition to complex patterns of coinciding electrical activities. While the precise functions of these patterns of activity remain a matter of intense debate, it is clear that sleep has a fundamental role in the maintenance of brain health, plasticity, and healthy cognition.

An increase in the cortical firing rates and synchrony (Vyazovskiy et al., 2009) and slope and amplitude of evoked cortical responses occur during wakefulness (Vyazovskiy et al., 2008). Moreover, the mean expression levels of synaptic AMPARs and their phosphorylation levels, which indicate synaptic potentiation, are higher during wakefulness than during sleep in both rat cortex and hippocampus (Vyazovskiy et al., 2008), and in the mouse forebrain (Diering et al., 2017). Conversely, the frequency and amplitude of miniature excitatory postsynaptic currents (Liu et al., 2010), spine density, and number of AMPARs (Diering et al., 2017; Maret, Faraguna, Nelson, Cirelli, & Tononi, 2011; Vyazovskiy et al., 2008; Yang & Gan, 2012) decrease during sleep. Recent ultrastructural studies of the mouse motor and sensory cortices have shown that the axon-spine interface is decreased – indicative of decreased synaptic strength (Nishiyama & Yasuda, 2015) – after sleep than after the wakeful period (Cirelli & Tononi, 2020; de Vivo et al., 2017). In addition, in adolescent mice, waking time is associated with an increase in synapse density and axon-spine interface in the hippocampus (Spano et al., 2019). Taken together, these and other findings highlight the strong synaptic regulation that occurs during wake and sleep. Because the antidepressant-like effects of ketamine seem to require AMPARs and are associated with changes in synaptic proteins and increased synaptogenesis, the possibility exists that unforeseen consequences emerge from the interaction of ketamine with the homeostatic mechanisms associated with wakefulness and sleep.

The effects of ketamine may also be modulated by homeostatic pressure and/or circadian time at the time of administration, as has been previously suggested by animal studies investigating the anesthetic effects of ketamine (Giedt, Lakin, & Winters, 1978; Rebuelto et al., 2002). In this context, the intrinsic regulation of cortical excitability may be particularly important because it influences the basal functionality of a given circuit and the circuit's response to an external stimulus. Indeed, it is now known that prolonged wakefulness leads to changes in cortical excitability, which is not only important for normal brain function and cognition but may also influence the pharmacological effects of drugs targeting the nervous system. For example, treatments given early in the morning may produce different outcomes than those given late in the evening, because cortical excitability is regulated by circadian rhythmicity (Ly et al., 2016) as well as wake and sleep (Kuhn et al., 2016). Thus, all therapeutics that elicit their primary effects through the regulation of, for example, excitatory neurotransmission may be modulated according to the time of administration and the basal state of the brain. Additionally, an excitatory stimulus may lead to different circadian responses depending on the time of day it is experienced (De Coursey, 1960; Khalsa, Jewett, Cajochen, & Czeisler, 2003; Pittendrigh, 1988). Stronger cues either advance or postpone the circadian rhythm, depending on whether they are experienced in the morning or evening, respectively. Timing may also contribute to many of the studies addressing antidepressant effects using functional imaging methods: a recent study suggested an association between time of day

and paradoxical reductions in global signal fluctuation and functional connectivity in humans (Orban, Kong, Li, Chee, & Yeo, 2020). In addition, brain glucose utilization measured using positron emission tomography undergoes significant diurnal variation, which is altered in depressed patients (Germain et al., 2007). Remarkably, the effect of experiment timing in subanesthetic ketamine or other rapid acting treatments of depression has not been clinically addressed; however, such studies have been planned (Zhuo et al., 2019).

A significant impact of treatment timing would indicate that many of the studies on the effects of ketamine in animal models, on multiple levels of inquiry, are only representative of the underlying basal conditions. Although sleep and circadian regulation likely serve similar functions in all animals, several features of the sleep-wake cycle, such as sleep architecture and circadian rhythms, are significantly different in humans and widely used experimental animals. Humans are diurnal and commonly sleep in one consolidated period during the dark phase. However, rodents undergo a polyphasic, segmented sleep rhythm and sleep in multiple shorter bouts throughout the 24 hours (Le Bon et al., 2007). Most importantly, in contrast to humans, most laboratory rodents are nocturnal and sleep predominantly during the light phase. Two-thirds of segmented sleep cycles occur during the light hours (i.e. the inactive period). As the remaining third of the time spent asleep occurs during the dark phase, the distinction between day and night is not as explicit in rodents as in humans. However, in preclinical research, animal handling and treatments are generally conducted during standard laboratory hours during the day, which corresponds to the inactive phase of nocturnal rodents and when the animals exhibit high sleep pressure (Alitalo, Saarreharju, Zarate, Kohtala, & Rantamaki, 2020). To date, this discrepancy has received very little attention in the field despite an abundance of evidence suggesting the involvement of sleep and circadian mechanisms.

It is important to acknowledge the effect of an activating stimulus during a period when the animals prefer to sleep. Indeed, in rodents, lower doses of ketamine are commonly found to stimulate locomotor activity – a strong non-photoc entrainment cue (Chang et al., 2019; Usun, Eybrard, Meyer, & Louilot, 2013; Yamamoto et al., 2016). Moreover, in rats, subanesthetic doses of ketamine acutely inhibit REM sleep, increase high-frequency gamma oscillations (52–100 Hz) and alter the dynamics of theta-gamma phase-amplitude coupling (Ahnaou, Huysmans, Biermans, Manyakov, & Drinkenburg, 2017). However, the interpretation of studies involving certain effects of ketamine is complicated owing to the variance in stimulatory responses according to sex and age of the animals (Crawford et al., 2020). Nevertheless, these studies imply that subanesthetic doses of ketamine are likely to disrupt physiological patterns of sleep, especially when delivered during the inactive period. Other excitatory stimuli, ranging from bright light (Benloucif, Masana, & Dubocovich, 1997) to electroconvulsive shocks (Quigg, Straume, Smith, Menaker, & Bertram, 2001), induce circadian phase shifts. In both rodents and humans, a light impulse experienced in early inactive period leads to a delay in circadian phase and therefore increased sleep latency. Considering that light-induced shifts in circadian phase are mediated by glutamatergic neurotransmission (Ebling, 1996; Mintz, Marvel, Gillespie, Price, & Albers, 1999), it is possible to speculate the nature of the effects of subanesthetic ketamine that lead to a glutamate burst. Unfortunately, there is a lack of research on the consequences of such disruption in the context of ketamine for the interpretation of behavioral or molecular studies. Nevertheless, it is well known that SD has antidepressant-like effects – similar to traditional antidepressants – in behavioral assays in animals, such as the forced swim test. In one study, rats subjected to total sleep deprivation for 24 hours demonstrated increased swimming behavior immediately afterwards as well as 48 hours later (Lopez-Rodriguez, Kim, & Poland, 2004). Similarly, REM sleep deprivation decreases immobility

(Hawkins et al., 1980; Van Luitelaar & Coenen, 1985). In light of the activity-promoting effects of ketamine and its ability to acutely suppress REM sleep and modulate circadian rhythms, it remains plausible that ketamine administered during the inactive phase has complex interactions with these systems, often remaining unaccounted for in basic research. Indeed, the need for an improved understanding of this topic is exemplified in recent research regarding the difference in the effects of rapastinel and ketamine on animal behavior and electrophysiology (Banerjee, Donello, Hare, & Duman, 2020); ketamine produces increased locomotor activity and a significant increase in sleep latency, because the treatments were administered early in the light phase. According to EEG activity, the animals still exhibit a high amount of SWS during their normal activity period, reflective of residual sleep pressure from the earlier sleep deprivation. Banerjee et al. (2020) discuss this phenomenon to support that rapastinel has a more beneficial side-effect profile than ketamine; however, they do not consider the effect of time of drug administration on their results. In this case, and perhaps other cases, the effects attributed solely to ketamine could therefore be masked – to a certain extent – by those of sleep disruption or deprivation, likely constituting a major confounding factor in studies investigating the effects of ketamine on depressive-like behavior, associated molecular pathways, and electrophysiological changes.

5. Closing remarks

The main purpose of this review is to call attention to chronobiological processes, especially sleep, in the mechanisms of action of ketamine and other treatments capable of producing rapid and sustained antidepressant effects. Combining the various known effects of ketamine with the regulation of sleep and wake may be instrumental in depicting the fundamental underpinnings of its therapeutic effects. Several recent hypotheses of rapid antidepressant action have emerged, where sleep or circadian rhythms are considered to play a crucial role. These new perspectives warrant further interest and examination from researchers from various backgrounds, such as pharmacologists, molecular neurobiologists, and sleep researchers. Indeed, only time – and meticulous scientific research – will tell how sleep and circadian regulation are associated with the antidepressant effects of ketamine and whether it is one of the last pieces of the puzzle necessary to gain a more comprehensive understanding of ketamine's actions in the brain.

Authorship contributions

O.A., S.R., M.R., S.K., and T.R. wrote or contributed to the writing of the manuscript. O.A. prepared figures and other artwork.

Declaration of Competing Interest

T.R. and S.K. are listed as co-inventors on a patent application wherein in new tools enabling the development of rapid-acting antidepressants and the efficacy monitors thereof are disclosed based on the basic principles of ENCORE-D. T.R. and S.K. have assigned their patent rights to the University of Helsinki but will share a percentage of any royalties that may be received by the University of Helsinki. All other authors declare that there are no conflicts of interest.

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